Is Canada missing out? An assessment of drugs approved internationally between 2016 and 2020 and not submitted for Health Canada review

Étienne Gaudette PhD, Shirin Rizzardo RPh MSc, Sasha B. Wladyka MBA MSc, Tuhin Rahman MA, Kevin R. Pothier BSc Pharm RPh

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In 2021, Canada ranked fourth among Organisation for Economic Co-operation and Development countries for per-person pharmaceutical spending, behind the United States, Japan and Germany[1] (Canada spent Can$1088, converted from US dollars using the Bank of Canada's annual average exchange rate). Despite these high pharmaceutical spending levels, studies have shown that fewer new drugs are launched in Canada than in the US and some European countries.[2–4] Although a mechanism exists to provide limited access to drugs available outside Canada when conventional therapies have failed or are unavailable,[5] people in Canada may be concerned about access to innovative drugs and ask whether the drugs that are not launched in Canada could provide substantial health benefits if they were available through conventional means. Because we are not aware of any study that has scrutinized drugs not launched in Canada, we sought to take a first step in assessing these drugs and determining whether their limited access warrants concern. We draw from multiple data sources to identify the drugs that were approved by the US and Europe between 2016 and 2020 but not submitted for Health Canada review, investigate their characteristics and indications, and appraise their availability and sales in peer countries.

Key points

- One-third of the new active substances approved in the United States and Europe between 2016 and 2020 had not been submitted for Health Canada review by February 2023.
- However, more than three-quarters of the new active substances not submitted for review would have joined 6 or more similar drugs marketed in the same therapeutic class in Canada.
- All but 1 of those substances reviewed by Germany's counterpart to the Canadian Agency for Drugs and Technologies in Health were found to provide no added therapeutic benefit relative to existing treatments.
- Of the new active substances not submitted in Canada, 60% recorded no sales in 2021 in a group of 11 peer countries. Most of those that recorded sales showed less than Can$10 million in total sales in these countries.
- The findings of this analysis suggest that most of the new active substances not submitted for Health Canada review would reach few Canadians and would have a limited health impact.

Of new drugs approved in the US and Europe, how many do not come to Canada?

We examined submissions of new active substances for Health Canada approval and found that, at most, one-third of those with a recent international approval are not submitted for approval in Canada. Submissions are indicative of the intent of manufacturers to bring new products to Canada, whereas their actual launch and formulary listing status are affected by Health Canada's review outcome and public and private drug plans, respectively (Figure 1).

Of 230 new active substances with an approval by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) or both between 2016 and 2020, 154 (67%) had been submitted for Health Canada approval by Feb. 10, 2023 (Figure 2). Of those, 142 (92%) received a Notice of Compliance (NOC), 8 (5%) were under review and 5 (3%) were cancelled by the sponsor or received a Notice of Non-Compliance, meaning that the submission was found to be incomplete or noncompliant with the requirements of the *Food and Drugs Act*.[11]

The remaining 75 new active substances (33% of those approved by the FDA or the EMA or both) had not yet been submitted for Health Canada review. However, important delays have been documented in the submission of drugs to different international agencies,[12] and a subset of the new active substances not submitted in Canada — especially those with a first international approval toward the end of our study window — is likely to be filed for review in the coming years. Although it is impossible to predict with certainty, we can reasonably expect the longer-term submission rate of new active substances to exceed two-thirds and reach 70%–80%.

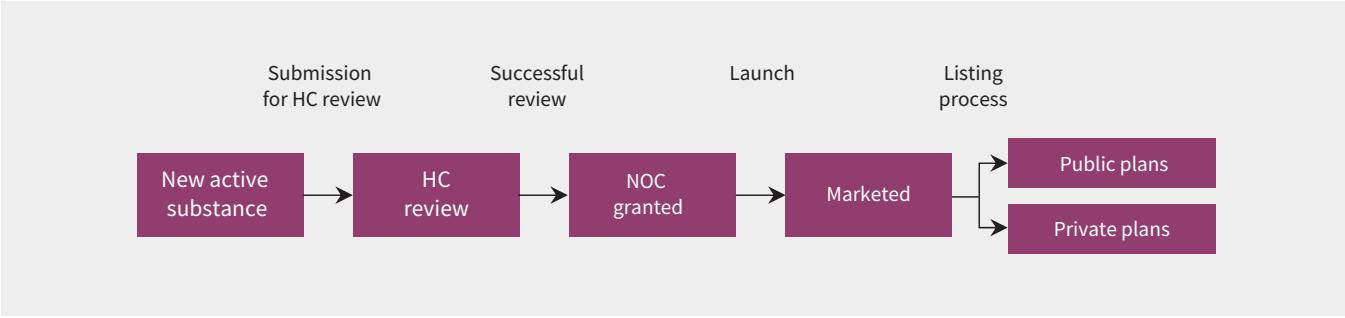

Figure 1: Launch and diffusion process of new active substances in Canada. Note: HC = Health Canada, NOC = Notice of Compliance.

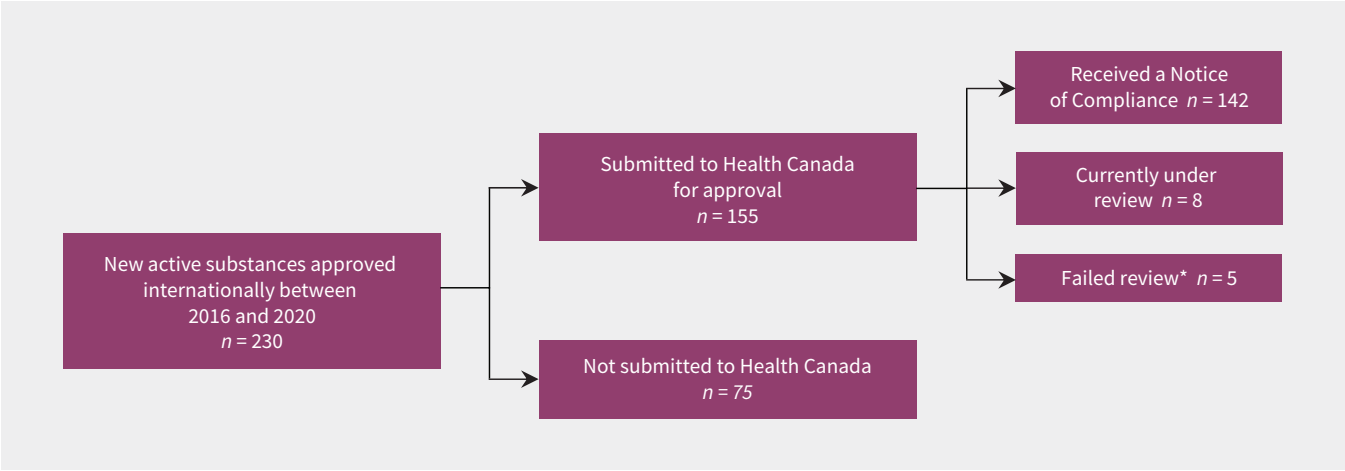

Figure 2: Health Canada submission status of new active substances, 2016–2020.*Four submissions were cancelled by the sponsor and 1 received a Notice of Non-Compliance. As of Feb. 10, 2023. Sources: *Meds Entry Watch* 2016, 2017, 2018, 5th and 6th editions;[6–10] Health Canada's *Notice of Compliance* database; Health Canada's *New Drug Submissions Completed* website; and Health Canada's *New Drug Submissions Under Review* website. Note: We defined new active substances as active medicinal ingredients with a first regulatory approval from Health Canada, the US Food and Drug Administration or the European Medicines Agency during the inclusion period. We also considered combination products to be new active substances if at least 1 of their active ingredients met that criterion. We used *Meds Entry Watch* reports for years 2016–2020[6–10] to identify 230 pharmaceuticals, which we included in the analysis. We excluded 2 substances listed in the reports because they received Health Canada Notices of Compliance under alternate brand names before 2016: Smallpox and Monkeypox Vaccine, Live, Non-Replicating, and Coagulation Factor VIIA (recombinant).

What kinds of new active substances are not submitted for approval in Canada?

We found that the new active substances not yet submitted for Health Canada approval are mainly from small manufacturers, indicated for modest patient populations, with multiple related drugs already marketed in Canada, or with no additional benefit relative to existing treatments. Table 1 shows trends in the characteristics, indications, approval status and sales levels in peer countries of the new active substances not submitted for Health Canada approval, as listed in Appendix 1, Table 1 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230339/tab-related-content).

Less than one-quarter (n = 18) of new active substances not submitted in Canada were licensed by a manufacturer ranked in the top 25 by market capitalization. About half (n = 37) were indicated for rare diseases and received an orphan designation from the EMA or the FDA, and 11 were indicated for diseases to affect fewer than 5000 patients in the US, as estimated by the National Institutes of Health. More information on the characteristics of the new orphan substances not submitted in Canada is presented in Appendix 1, Table 2. Of the 17 infectious disease treatments in the new active substances list, 8 were antibiotics or add-ons to antibiotics with indications to be used in specific or complicated cases. Given that Canada has one of the lowest drug resistance indexes, second only to Sweden,[14] there may be limited clinical need for these therapies. A further 6 were indicated for diseases that have a low incidence in Canada (e.g., plasmodium vivax malaria, hepatitis D and Chagas disease).

In most cases, multiple drugs in the same therapeutic class and with a similar chemical profile were already available to Canadians. For 58 (77%) of the new active substances not submitted in Canada, more than 5 drugs were marketed in Canada in the same pharmacologic subgroup (Table 1). This classification level groups drugs with a similar chemical profile indicated for the same therapeutic class and corresponds to the third level of the World Health Organization Anatomic Therapeutic Chemical classification system code (ATC3). Not all drugs within an ATC3 treat the same indication. Some ATC3s are broadly defined and

Table 1: New active substances not submitted to Health Canada, by drug characteristic and indication, international approval status and 2021 sales levels in PMPRB11 countries and the United States

Characteristic	No. (%) of new active substances
Substances not submitted to Health Canada	75 (100)
Substances by characteristic and indication category	
Top 25 manufacturer*†	18 (24)
Biologic†	21 (28)
Oncology indication†	13 (17)
Infectious disease indication†	17 (23)
Orphan designation†	37 (49)
US prevalence < 5000‡	11 (15)
Multiple indications†§	11 (15)
Substances by number of DINs approved for sale in Canada in the same pharmacologic subgroup¶	
6 or more DINs	58 (77)
1–5 DINs	2 (3)
0 DIN	5 (7)
Unknown pharmacologic subgroup	10 (13)
Substances by IQWiG benefit assessment relative to existing therapies**	
Proof of nonquantifiable added benefit	1 (1)
Added benefit not proven	13 (17)
Not assessed	61 (81)
Substances by FDA and EMA approval status††	
Approved by both the FDA and the EMA	31 (41)
FDA only	33 (44)
EMA only	7 (9)
None (withdrawn approval)	4 (5)
Substances by sales in PMPRB11 countries	
Sold Can$100 million or more	2 (3)
Sold less than Can$100 million	28 (37)
No sales	45 (60)
Substances by US sales	
Sold Can$100 million or more	10 (13)
Sold less than Can$100 million	42 (56)
No sales	23 (31)
Substances that recorded no sales in PMPRB11 countries and US	17 (23)

Note: ATC = Anatomic Therapeutic Chemical, DDD = defined daily dose, DIN = Drug Identification Number, EMA = European Medicines Agency, EPAR = EMA Human Medicine European public assessment report, FDA = United States Food and Drug Administration, IQWiG = Institute for Quality and Efficiency in Health Care, NIH GARD = National Institutes of Health Genetic and Rare Disease Information Center, PMPRB = Patented Medicine Prices Review Board, PMPRB11 = 11 comparator countries: Australia, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Sweden and the United Kingdom.
*We identified the top 25 manufacturers using GlobalData Pharmaceutical's Global: Companies by Market Cap list.[13]
†The biologic, oncology indication, infective disease indication, orphan indication and multiple indications characteristics were nonexclusive. We took biologic and oncology status from the *Meds Entry Watch* report first listing the new active substances. We assessed indications from Jan. 16–19, 2023, using the EMA EPAR or the most recent FDA drug label.
‡We determined the US prevalence by conducting keyword searches of the indication(s) listed on the drug label of a drug with an FDA orphan indication on the NIH GARD website.
§We assigned a multiple indication status if more than 1 indication was listed on the EPAR or on the most recent FDA drug label.
¶We defined pharmacologic subgroups by the third level of the World Health Organization classification system (ATC3) code of the drug, assessed using the EPAR or the ATC/DDD Index 2023 website. We determined the number of DINs approved for sale in Canada by counting DINs with the same ATC3 code approved for sale using a Feb. 1, 2023, extract of the Health Canada Drug Product Database.
**We extracted IQWiG benefit assessments from the agency's annual *Zusatznutzen: Ja oder Nein?* reports.
††We assessed FDA and EMA approval status from Jan. 16–19, 2023.
Sources: *Meds Entry Watch* 2016, 2017, 2018, 5th, and 6th editions,[6–10] GlobalData, Drugs@FDA, EMA, NIH GARD, Health Canada *Drug Product Database*, IQWiG and IQVIA MIDAS.

feature drugs that treat a cluster of related but distinct indications. Of the 7 new active substances with 5 or fewer drugs currently marketed in Canada in their pharmacologic subgroup, only 2 showed sales in the US or a group of 11 peer countries used for international price comparisons of patented medicines by the Patented Medicine Prices Review Board (PMPRB11). These were istradefylline, indicated in adjunctive treatment to levodopa–carbidopa in adult patients with Parkinson disease, and osilodrostat, indicated for the treatment of endogenous Cushing disease in adults.

Of new active substances not submitted in Canada but reviewed by the Institute for Quality and Efficiency in Health Care (IQWiG), Germany's federal agency tasked with conducting health technology assessments, 13 (93%) were found to show no additional benefit relative to existing treatments. Only 1 drug (bezlotoxumab, indicated for the prevention of recurrence of *Clostridium difficile* infection) was assessed to have nonquantifiable added benefit.

How widely marketed in peer countries are the new active substances not submitted to Health Canada?

In large part, these new active substances are not widely marketed in peer countries, except for the US. For the 75 new active substances not submitted for Health Canada review, we investigated whether sales were recorded internationally in the IQVIA MIDAS database in calendar year 2021, which allowed for at least 1 full year of diffusion after a first international approval for all 75. MIDAS data reflect the national retail and hospital sectors internationally, including payers in all market segments (public, private and out of pocket).

In 2021, 45 of the 75 new active substances not submitted to Health Canada (60%) did not record sales in PMPRB11 peer countries (Figure 3). Of those that recorded sales, 26 were sold in fewer than half (≤ 5) of comparator countries and 4 recorded sales in more than half (≥ 6) of comparator countries. On average, those substances not submitted to Health Canada recorded sales in just 1.3 PMPRB11 countries. None recorded sales in all comparator countries.

Among comparator countries, Germany sold the most new active substances that were not submitted to Health Canada with 19 (25%), while the median country sold 8 (11%; Figure 4). Only 2 of the PMPRB11 countries, Japan and Australia, are not represented in the EMA and, like Canada, have their own drug approval body. Japan recorded sales for 14 of the new active substances not submitted to Health Canada (19%), and Australia recorded sales for 1 (1.3%). We included the US in the figure for context, given its geographic proximity to Canada and its status as a global outlier in both pharmaceutical spending and adoption of new drugs.[1,3,10] The US recorded sales for 52 (69%) of the new active substances not submitted to Health Canada.

Most new active substances sold in PMPRB11 countries in 2021 showed less than Can$10 million in sales across these

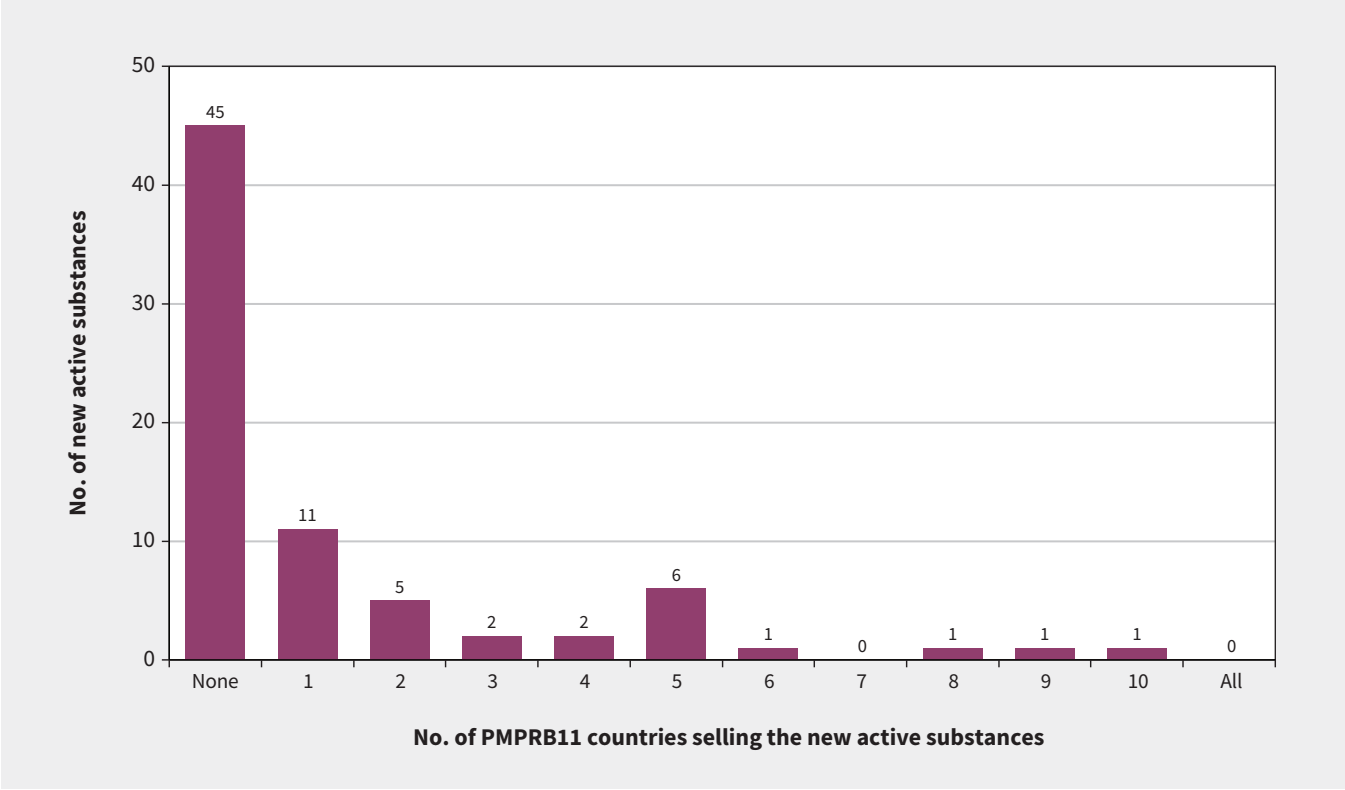

Figure 3: Sales of new active substances not submitted to Health Canada in 11 Patented Medicine Prices Review Board (PMPRB11) comparator countries, 2021. Note: PMPRB11: Australia, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Sweden and the United Kingdom. Source: IQVIA MIDAS database.

countries (n = 18/30 [60%]), and only 2 recorded more than Can$100 million in sales (Table 1). The highest-selling product was etelcalcetide, used in the treatment of hyperparathyroidism for patients on dialysis in 10 PMPRB11 countries. As of Feb. 1, 2023, Canada had 29 drugs marketed in etelcalcetide's pharmacologic subgroup, H05B (calcium homeostasis) (Appendix 1, eTable 1). The second was vibegron, indicated for the treatment of overactive bladder; the only PMPRB11 country with sales of this drug was Japan. Canada had 178 drugs marketed in the related G04B (urologicals) pharmacologic subgroup. A pharmacologic subgroup could not be identified for vibegron because it was not assigned an ATC code.

Should people in Canada be worried about access to innovative drugs?

Our analysis of the characteristics of new active substances not yet submitted for Health Canada approval provides some insight into the types of medicines that manufacturers choose not to introduce to Canada. First, most unsubmitted new active substances were produced by relatively small manufacturers, which may be constrained in their capacity to prepare multiple submissions to international regulators and therefore prioritize submissions to the FDA and the EMA, which provide access to larger patient populations. This would be consistent with previous findings of longer submission delays to Health Canada for smaller companies.[12]

Second, whether most of these new active substances would be considered therapeutically innovative or answer unmet needs in Canada is unclear. According to their ATC code, more than three-quarters would join pharmacologic subgroups with more than 5 drugs currently marketed in Canada. This means that multiple offerings in the same therapeutic class and with a similar chemical profile are available to Canadians, although the specific indications for treatment may differ. In addition, all but 1 of those reviewed by IQWiG in Germany were found to have no additional therapeutic benefit relative to existing treatments.

Third, most of the new active substances that were not submitted in Canada have not recorded sales in the group of countries used as comparators by the PMPRB, and only 4 recorded sales in more than half of these countries. Their low utilization in peer countries suggests a small market for these pharmaceuticals in Canada, which may have contributed to the manufacturers' decisions not to make a Health Canada submission.

We acknowledge that our findings may have been affected by the COVID-19 pandemic, which has had complex effects on the pharmaceutical industry internationally since 2020. On one hand, manufacturers may have submitted fewer new active substances to Health Canada than they would have otherwise. On the other, marketing of new medicines may have been delayed, resulting in fewer unsubmitted medicines being marketed in peer countries by 2021. In addition, because we focused on Health Canada submissions, we did not investigate Health Canada review results, launches, formulary listing decisions and

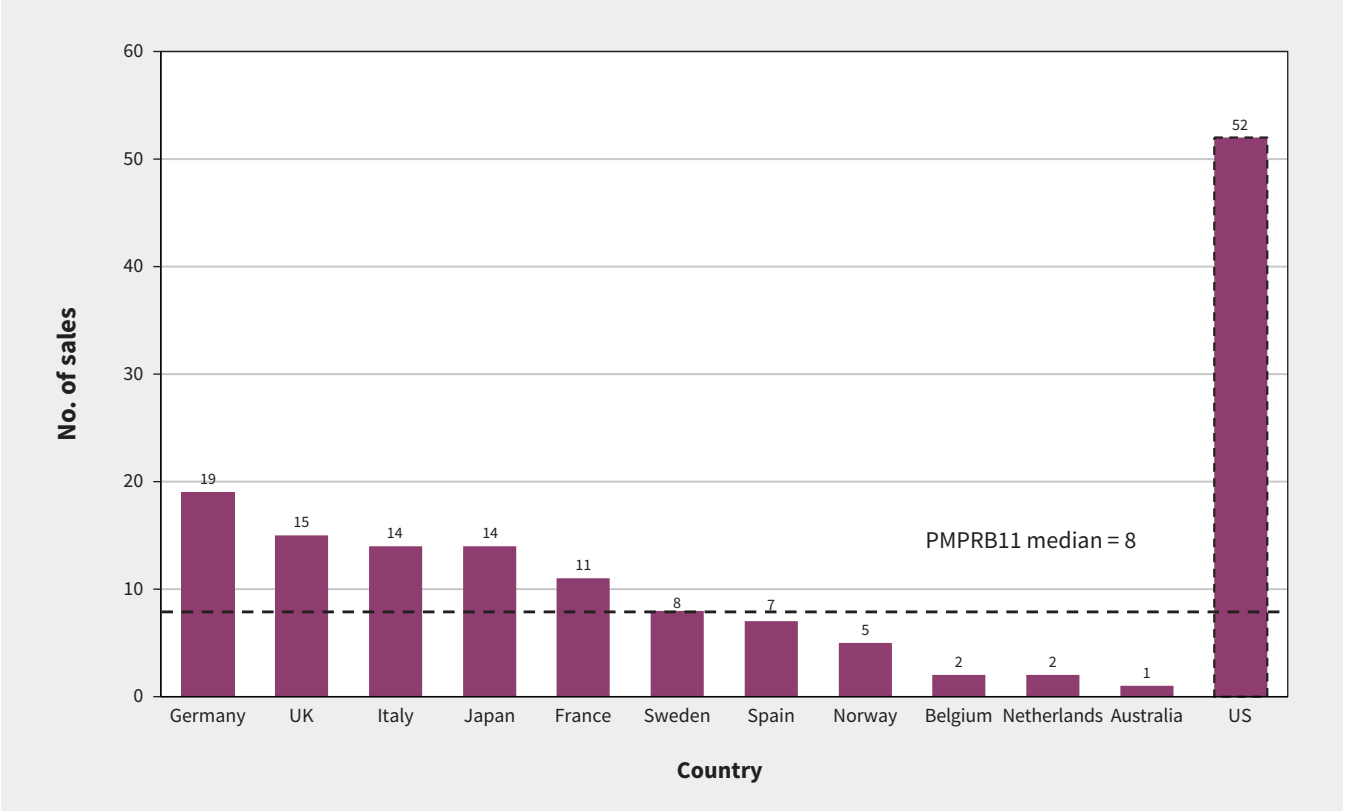

Figure 4: Distribution of 11 Patented Medicine Prices Review Board (PMPRB11) comparator countries and the United States by number of new active substances not submitted to Health Canada with sales, 2021. Source: IQVIA MIDAS database.

delays, which can also contribute to limiting access to new active substances for people in Canada.

Furthermore, some of the new active substances that were not submitted in Canada could provide important benefits to specific populations despite being used chiefly in the treatment of diseases with low prevalence and not being launched widely in other countries. Although access to pharmaceuticals not marketed in Canada is possible through Health Canada's Special Access Program for drugs, this mechanism is restricted to "the treatment, diagnosis, or prevention of serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable," and Special Access Program requests may not be approved in all cases.[5]

A thorough review of the clinical impacts of each new active substance not submitted for Health Canada approval could provide a better understanding of the health consequences of limitations to their access. However, our analysis suggests that most of them would reach few Canadians and would have a limited health impact if they were approved.

References

1. Pharmaceutical spending (indicator). Paris (FR): Organisation for Economic Co-operation and Development; 2023. Available: https://data.oecd.org/healthres/pharmaceutical-spending.htm (accessed 2023 Feb. 2).
2. Outterson K, Orubu ES, Rex J, et al. Patient access in 14 high-income countries to new antibacterials approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020. *Clin Infect Dis* 2022;74:1183-90.
3. Spicer O, Grootendorst P. The effect of patented drug price on the share of new medicines across OECD countries. *Health Policy* 2022;126:795-801.
4. Ward LM, Chambers A, Mechichi E, et al. An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries. *Orphanet J Rare Dis* 2022;17:113.
5. Special Access Program for drugs: guidance document for industry and practitioners. Ottawa: Health Canada; 2022. Available: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf (accessed 2023 Mar. 9).
6. *Meds Entry Watch*, 2016. Ottawa: Patented Medicine Prices Review Board; 2018. Available: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1374 (accessed 2023 Feb. 8).
7. *Meds Entry Watch*, 2017. Ottawa: Patented Medicine Prices Review Board; 2019. Available: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1428 (accessed 2023 Feb. 8).
8. *Meds Entry Watch* 2018. Ottawa: Patented Medicine Prices Review Board; 2020. Available: https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/meds-entry-watch-2018.html (accessed 2023 Feb. 8).
9. *Meds Entry Watch*, 5th edition. Ottawa: Patented Medicine Prices Review Board; 2021. Available: https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/meds-entry-watch-5th-edition.html (accessed 2023 Feb. 8).
10. *Meds Entry Watch*, 6th edition. Ottawa: Patented Medicine Prices Review Board.; 2022. Available: https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/meds-entry-watch-6th-edition.html (accessed 2023 Feb. 8).
11. Guidance document: management of drug submissions and applications. Ottawa: Health Canada; 2022. Available: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry/guidance-document-management-drug-submissions-applications.pdf (accessed 2023 Apr. 13).
12. Shajarizadeh A, Hollis A. Delays in the submission of new drugs in Canada. *CMAJ* 2015;187:E47-51.
13. Global Data Pharmaceuticals: Companies. GlobalData. Available: https://pharma3.globaldata.com/Company/Search (accessed 2023 Feb. 1). Login required to access content.
14. Klein EY, Tseng KK, Pant S, et al. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. *BMJ Glob Health* 2019;4:e001315.

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Affiliations: Institute of Health Policy Management and Evaluation (Gaudette), University of Toronto, Toronto, Ont.; Patented Medicine Prices Review Board (Gaudette, Rizzardo, Wladyka, Rahman, Pothier), Ottawa, Ont.

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Correspondence to: Étienne Gaudette, etienne.gaudette@utoronto.ca